Optison™

(perflutren protein-type A microspheres injectable suspension)

GE Healthcare

Introduction and Optison Post-Marketing Safety Data

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Objectives

- **Demonstrate safety of**
  - **Post-marketing surveillance**
  - **Literature**
  - **Recent studies**
- **Describe impact of Boxed Warning**
  - **Reduced access to patients in need**
- **Recommend removal of Boxed Warning**
  - **Warnings already addressed in package insert**
  - **Reformat to better highlight Warnings and Contraindications**

Overview of Presentation

	Topic	Presenter	Affiliation
1.	Introduction and Optison Post-Marketing Safety Data	Paul Sherwin, MD, PhD	GE Healthcare
2.	Post-Marketing Clinical Studies of Optison Safety	Jonathan Goldman, MD, FACC, FASE	ICON, Clinical Research UCSF
3.	Peer-Reviewed Literature on Optison Human Safety	Steven Feinstein, MD, FACC, FESC	Rush University Medical Center
4.	Impact of Product Labeling on Patient Care	Steven Feinstein, MD, FACC, FESC	Rush University Medical Center
5.	Conclusions	Paul Sherwin, MD, PhD	GE Healthcare

Ultrasound Contrast Agents (UCA)

- **UCA are sterile suspensions of microspheres**
  - **Shell: albumin or phospholipid**
  - **Gas: perflutren**
- **UCA reflect ultrasound waves during echo procedures**
  - **Increasing blood-tissue contrast**
  - **Improving visualization of ventricular walls (diagnostic benefit)**

Two Approved UCA in USA

Product	Optison	Definity
Indication	In suboptimal echo, to opacify LV chamber, improve delineation LVEB	
Not indicated for	Exercise stress Pharmacologic stress	
Contraindications	Right-to-left shunts Perflutren hypersensitivity Intra-arterial injection (Optison only: hypersensitivity to blood, blood products, albumin)	
Microsphere Concentration	5 to 8 x 10^8 per mL	Up to 1.2 x 10^{10} per mL
Microsphere Diameter (μm)	Mean 3.0 to 4.5 95% < 10	Mean 1.1 to 3.3 98% < 10

Two Approved UCA in USA (continued)

Product	Optison (1997)	Definity (2001)
Shell	Albumin	Phospholipid
Gas	Perflutren (octafluoropropane)	
Gas Elimination Half-life	1.3 min (complete elimination in 6 to 10 min)	
Route of Gas Elimination	Exhaled through lungs	
Dose	0.5 mL/injection (up to 5 mL/10 min; 8.7 mL total)	10 μL/kg/injection (up to 2 injections) (Infusion 1.3 mL/ 50 mL NaCl)
Perflutren Gas Dose	25 μL/mL	150 μL/mL

Recent FDA Actions on UCA

- **2007 (Oct) Based on reports of 11 mortalities (1 following Optison use) and 199 serious non-fatal events (9 following Optison use)**
- **UCA labeling revised to add:**
  - **Boxed warning**
  - **Contraindications in patients with unstable cardiac conditions or pulmonary hypertension**
  - **Monitoring all patients 30 min. after dosing**

Recent FDA Actions on UCA (continued)

- **2008 (Mar) Based on 2 published studies: one Optison[1] (n = 57), one Sonovue[2] (n = 13)**
- **UCA risk in pulmonary hypertension may not be as high as previously thought**
- **UCA Labeling Modified**
  - **Monitoring required for high-risk patients instead of all patients**
  - **Majority of new contraindications removed**
- **Sponsors to conduct post-marketing safety studies**

Erb J, Shanewise J. Intraoperative contrast echocardiography with intravenous Optison does not cause hemodynamic changes during cardiac surgery. J Am Soc Echocardiography 2001;14;595-600.

Soman P, Lahiri A, Senior R. Safety of an intravenous second generation contrast agent in patients with severe left ventricular dysfunction. Heart 2000;84:634-5.

Optison Current Boxed Warning

- **Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren containing microsphere administration**
- **Assess all patients for the presence of any condition that precludes Optison administration (see CONTRAINDICATIONS)**
- **In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after Optison administration (see WARNINGS)**
- **Always have resuscitation equipment and trained personnel readily available**

Optison Post-Marketing Safety Data Summary

	Before Boxed Warning 1997-2008	After Boxed Warning 2008-2010**	Overall
Patient Exposure	1,095,000	55,000	1,150,000
Non-Fatal Serious AE	11 (0.001%)	6*** (0.011%)	17 (0.0015%)
Fatal Serious AE	1* (0.00009%)	0 (0%)	1** (0.00009%)

*Pericardial effusion due to myocardial rupture following dobutamine stress test 3 days post-acute MI

**Optison off-market from 11/2005 to 11/2007 and 6/2009 to 7/2010

***Found through GE literature surveillance

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5.	**Conclusions**	Paul Sherwin, MD, PhD	GE Healthcare

Post-Marketing Commitment Safety Studies

Jonathan Goldman, MD, FACC, FASE
ICON, Clinical Research
Executive Vice President

University California San Francisco
Assistant Clinical Professor of Medicine
Staff Medical Cardiologist, SFVA

Overview of Studies

Study No.	Main Objective
GE-191-003	SARs in Optison patients
GE-191-004	Effects on Pulmonary Arterial Systolic Pressure (PASP) and Pulmonary Vascular Resistance (PVR)
GE-191-005	1-day and 2-day in-hospital mortality in critically ill patients

GE-191-003: Study of SARs in Optison Patients

Objective	**Assess SAR rate in patients who receive Optison in routine medical practice**
Design	**Prospective open-label uncontrolled**
Population	**1,039 adults scheduled for clinically indicated Optison echo from Jun 2008 to Mar 2009 at 18 US centers**
IV Optison Dose	**Per clinical need**
Primary Outcome Measure	**Rate of SARs; DSMB-assessed causality for fatal or life-threatening AEs**

GE-191-003: Subject Demographics and Dosing

	N = 1,039
Male	62%
Age	20-97 (mean 59)
White Black Asian	83% 14% 2%
BMI	15-82 (mean 34)
Total Optison Dose	0.2 to 10 mL (mean 1.91 mL)
Stress Procedure(s) (off-label)	47%

GE-191-003 Results

- No deaths or Serious Adverse Reactions
- 5 patients experienced a total of 6 SAEs, none deemed related to Optison by investigator, GE, or DSMB
- Vital signs (systolic and diastolic blood pressure, heart rate and respiration rate) generally stable from baseline until 1 hour post injection

GE-191-003: Serious Adverse Events

- **Non-sustained ventricular tachycardia (ended when dobutamine stopped)**
- **Fluid overload and sustained ventricular tachycardia after 9-hr RF ablation procedure**
- **Diagnosed by CEUS:**
  - **Coronary artery disease**
  - **LV thrombus**
  - **LV tumor**

No SAE was deemed related to Optison by investigators, GE, or the DSMB

GE-191-003: Summary of All Adverse Events

AE Incidence (N = 1,039)	**Any**	**17%**
	Cardiovascular	**13%**
	Pulmonary	**7%**
	Other	**2%**
Causality (N = 175)	**Suspected**	**1%**
	Not suspected	**99%**
Intensity (N = 175)	**Mild**	**83%**
	Moderate	**7%**
	Severe	**2%**
	Not assessed	**8%**

*AE types cannot be added; subjects may have had more than 1 AE type.

Tables 14.3.1.1a, 14.3.1.3a, 14.3.1.6a, and 14.3.2.1a; Listing 16.2.7.1

GE-191-003: AE Subgroup Analyses

Age	**< 65 years**	**18.5%**
	65 to 75 years	**14.5%**
	>75 years	**12.8%**
Gender	**Women**	**23.5%**
	Men	**12.8%**
Dose	**Direct relationship with AE rate; but higher cumulative doses used for stress echo**	
Echo Type	**Stress 13x higher than Rest**	

GE-191-003: AE Rates by Procedure Type

Adverse Event Type	Study 003 Stress n/N (%)	Study 003 Non-Stress n/N (%)	Package Insert (Non-Stress)
Cardiac	120/466 (26%)	10/536 (2%)	12/279 (4%)
Pulmonary	68/466 (15%)	0/536 (0%)	5/279 (2%)

GE-191-003: Conclusions

- **Optison generally safe and well-tolerated**
  - **No deaths or SARs**
  - **6 SAEs unrelated to Optison**
  - **Cardiopulmonary AEs were generally mild and unrelated to Optison**

GE-191-004: Prospective Randomized Control Study of Optison Effects on PASP and PVR

Objectives	Compare Optison and placebo for effects on pulmonary arterial systolic pressure (PASP) and pulmonary vascular resistance (PVR)
Design	Single-blind, cross-over, randomized placebo control
Population	30 adults scheduled for right heart cath May 2009 to July 2010, with either normal (< 35 mmHg; N = 15) or elevated (> 35 mmHg; N = 15) PASP
Exposure	Patients randomized to receive 1) 0.5 mL Optison followed 15 min later by placebo (5% dextrose), or 2) the reverse
Primary Outcome Measures	Changes in PASP and PVR at 2, 6, and 10 min post-dose

GE-191-004: Subjects

	Normal PASP N = 11*	Elevated PASP N = 19*
Screening PASP	22-35 (mean 29)	36-176 (mean 70)
Male	73%	32%
Age	49-78 (mean 64)	19-78 (mean 52)
White Black	82% 18%	79% 21%
BMI	22-35 (mean 29)	19-45 (mean 30)

*Changes in sample sizes agreed to by FDA

GE-191-004: Mean PASP Results (mmHg)

	Baseline	Time Point		
		2 Min Post	6 Min Post	10 Min Post
Elevated PASP Optison	68.3	68.2	66.9	66.0
Elevated PASP Control	65.5	65.6	66.5	67.5
Normal PASP Optison	32.5	33.9	33.0	32.8
Normal PASP Control	33.4	35.1	34.1	33.2

Difference between Optison and Control significant only at 10 min for elevated PASP (-4.26 mmHg [LS mean] in favor of Optison)
No clinically significant differences

GE-191-004: PVR Results (Woods units)

	Baseline	Time Point		
		2 Min Post	6 Min Post	10 Min Post
Elevated PASP Optison	4.9	5.0	4.6	5.1
Elevated PASP Control	5.3	5.4	5.1	4.7
Normal PASP Optison	1.6	1.8	1.5	1.5
Normal PASP Control	1.6	1.8	1.5	1.4

No clinically significant differences

GE-191-004: Other Safety Results

- No deaths, SAEs, or severe AEs
- One AE (procedural pain: catheter withdrawal)
- No clinically relevant changes in
  - Hemodynamic parameters
  - Vital signs
  - Oxygen saturation
  - Clinical laboratory tests
  - ECG findings

GE-191-004: Conclusions

- **Optison safe and well tolerated**
- **Did not increase PASP or PVR in subjects with normal or elevated PASP**
- **Results consistent with Optison study cited by FDA when revising package inserts in 2008 (Erb and Shanewise, 2001;57 patients):**

  "…injection of Optison did not cause any clinically important changes in parameters of hemodynamic stability and cardiac performance and did not influence oxygenation in patients undergoing surgery for CABG, valvular surgery, or combined procedures."

Erb J, Shanewise J. Intraoperative contrast echocardiography with intravenous Optison does not cause hemodynamic changes during cardiac surgery. J Am Soc Echocardiography 2001;14;595-600.

GE-191-005: Retrospective Study of 1-Day and 2-Day Mortality After Echocardiography

Objectives	**Compare mortality rates with and without Optison in critically ill patients**
Design	**Retrospective, matched control**
Population	**Critically ill patients (≥ 1 of 6 diagnoses related to Warnings in Optison insert) undergoing echo with either Optison or no contrast Jan 2003 to Nov 2005**
IV Optison Dose	**Per medical need**
Primary Outcome Measures	**1-day (same-day) and 2-day (same- or next-day) in-hospital mortality**

GE-191-005 Diagnoses Included vs. Labeled Warnings

005 Patients had ≥ 1 of the following ICD-9 diagnoses
Acute myocardial infarction
Pulmonary embolism
Pulmonary hypertension
Respiratory failure
Serious ventricular arrhythmias
Worsening or unstable CHF

GE-191-005: Selection of No-Contrast Controls

- **Inclusion criteria met by:**
  - **2,884 contrast (Optison) echo patients**
  - **207,066 no-contrast echo patients**
- **Optison and controls differed in 25/29 variables (demographics, indicators of clinical condition, medication usage, co-morbidities)**
- **14% of critically ill patients received Optison vs. 9% of non-critically ill patients**
- **Each contrast patient (N = 2,884) matched to 4 controls (N = 11,536) on the 29 variables**
  - **Propensity score and stepwise logistic regression**
  - **After matching, differences in 4/29 variables**

GE-191-005: Matching by Critical Diagnosis

- For meaningful results, it is crucial that contrast patients and controls have similar baseline mortality risks independent of treatment (contrast or no contrast)
- Although patients in control group had same 6 critical diagnoses, per-protocol matching of 4 controls to each contrast patient did not account for the critical diagnosis
- Result: most Optison patients were matched to control patients with another critical diagnosis
- Because mortality risk is not the same across the 6 critical diagnoses, this resulted in a mismatch of baseline mortality risk
- Therefore, an alternative method matched each contrast patient to 4 controls with same critical diagnosis

GE-191-005: Same-Day Mortality

	Odds Ratio	95% Confidence Intervals	
		Lower	Upper
GE Per-Protocol (No ICD matching) Contrast = 38 (1.3%) Control = 109 (0.94%)	1.400	0.965	2.030
GE Alternative Analysis (ICD matching) Contrast = 38 (1.3%) Control = 127 (1.1%)	1.208	0.833	1.752
FDA Analysis Contrast = 38 (1.3%) Control = 141 (1.2%)	1.16	0.80	1.68
GE Alternative Analysis with 3M APR-DRG indices Contrast = 38 (1.3%) Control = 136 (1.2%)	1.124	0.777	1.627

All show increased mortality in CEUS group that did not reach statistical significance
No deaths were reported to GE Healthcare

Different Definitions of Critical Illness

- **Optison**
  - ICD-9 codes matching at least 1 of 6 critical conditions
  - ICU and/or CCU stay were included in the propensity score model
  - However, patients were not limited to those in the ICU and/or CCU
- **Definity**
  - ICU and/or CCU, not ICD-9 code
  - ICD-9 code (comorbidity) was used in the propensity score model
- **This led to different patient cohorts**

Same-Day Mortality: Optison vs. Definity

	Odds Ratio (p-Value)	
	Optison	Definity
Per-Protocol (No ICD matching)	1.400 (0.0760)	1.338 (0.1628)
Alternative Analysis (ICD matching)	1.208 (0.3199)	1.123 (0.5775)
Alternative Analysis with 3M APR-DRG	1.124 (0.5343)	1.061 (0.7713)

All show increased mortality in CEUS group that did not reach statistical significance

GE-191-005: Same-Day Mortality Ventilated Subgroup

	Odds Ratio	95% Confidence Intervals	
		Lower	Upper
Alternative Analysis (ICD matching)			
Optison Contrast = 22/493 (4.46%) Control = 86/1,905 (4.51%)	0.903	0.512	1.594
Definity Contrast = 17/392 (4.34%) Control = 69/1,604 (4.30%)	0.979	0.540	1.774
Alternative Analysis with APR-DRG			
Optison Contrast = 22/493 (4.46%) Control = 94/2,088 (4.50%)	0.876	0.499	1.537
Definity Contrast = 17/392 (4.34%) Control = 72/1,584 (4.55%)	1.023	0.568	1.841

GE-191-005: Study Limitations

- Observational nature
- Treatment selection non-random
- Measurement of time of death (date rather than time of day)
- Cause of death not available
- Indication for echocardiogram not available
- Inherent selection bias

GE-191-005: Conclusion

- **There is no statistically or clinically relevant increase in same-day or two-day all-cause mortality for patients who received Optison**

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Peer-Reviewed Literature on Optison Human Safety Impact of Product Labeling on Patient Care

Steven B. Feinstein, MD, FACC, FESC

Professor of Medicine

Director – Echocardiography Lab

Rush University Medical Center

Chicago, IL

Evidence-based, Peer-reviewed Safety Data Regarding Optison

- **ICU/Operating Room studies** **2000-2002**
- **Peer-reviewed clinical studies** **2008-2010**
- **Meta analysis of safety studies for CEUS including >211,162 patients** **2010**

ICU Optison Safety Studies 2000-2002

- **3 prospective studies: 187 critically ill patients in ICU**
- **31-100% mechanically ventilated/supplemental O_2**
- **Repeated boluses of Optison**
- **No deaths, no changes in systolic/diastolic BP or O_2 saturation**
- **Each author recommended the safe use of Optison in ICU setting**

JP Reilly, et al. Contrast Echocardiography clarifies uninterruptable wall motion in intensive care patients, J AmColl Cardiol 2000;35:485-90

CK Daniel, et al. Echocardiographic imaging of technically difficult patients in the ICU, J Am Soc Echocardiogr 2001;14:917-20.

Y Yong, et al. Diagnostic accuracy and cost effectiveness of contrast echocardiography on evaluation of cardiac function in technically difficult patients in the ICU, Am J Cardiol 2002;89:711-718

Operating Room Optison Safety Study 2001

- **Goal: Benefit/risk and safety of CEUS in high risk patients**
- **35 patients undergoing cardiac surgery with continuous anesthesia received 97 injections of Optison in a central vein; the mean LV EF = 40%**
- **Monitoring: continuous ECG, arterial blood gases, CVP, pulse oximetry, BP, CI, and pulmonary artery pressure**
- **Conclusion: *"Optison did not cause clinically important changes in parameters of hemodynamic stability, cardiac performance, and oxygenation in our patients."***

J Erb, et al. Intra-operative contrast echocardiography with IV Optison Does Not Cause Hemodynamic Changes During Cardiac Surgery. J Amer Soc Echocardiogr 2001;14(9):595-600.

Operating Room Optison Safety Study: Results

- **35 heart surgery patients (CABG, ASA class IV), received 97 total injections of 0.3 mL bolus of Optison via a central venous catheter**
- **No statistically significant differences in pulmonary artery systolic pressure, airway pressures, blood pressure, oxygen saturation**

Sub-groups	Time of Measurements	PAs mmHg	PAd mmHg	End tidal CO_2 tension mmHg	
97 injections (n = 35 pts all ASA class IV*)	**5 min vs. baseline**	**1.3 ± 2.4**	**0.6 ± 2.4**	**30 ± 4**	**NS**
	10 min vs. baseline	**0.7 ± 5.0**	**0.9 ± 3.0**	**30 ± 4**	**NS**

*ASA class IV = Patients have severe systemic disease that limits activity and is a constant threat to life.

J Erb, et al. Intra-operative contrast echocardiography with IV Optison Does Not Cause Hemodynamic Changes During Cardiac Surgery. J Amer Soc Echocardiogr 2001;14(9):595-600.

Peer-reviewed, Optison Safety Studies 2008-2010

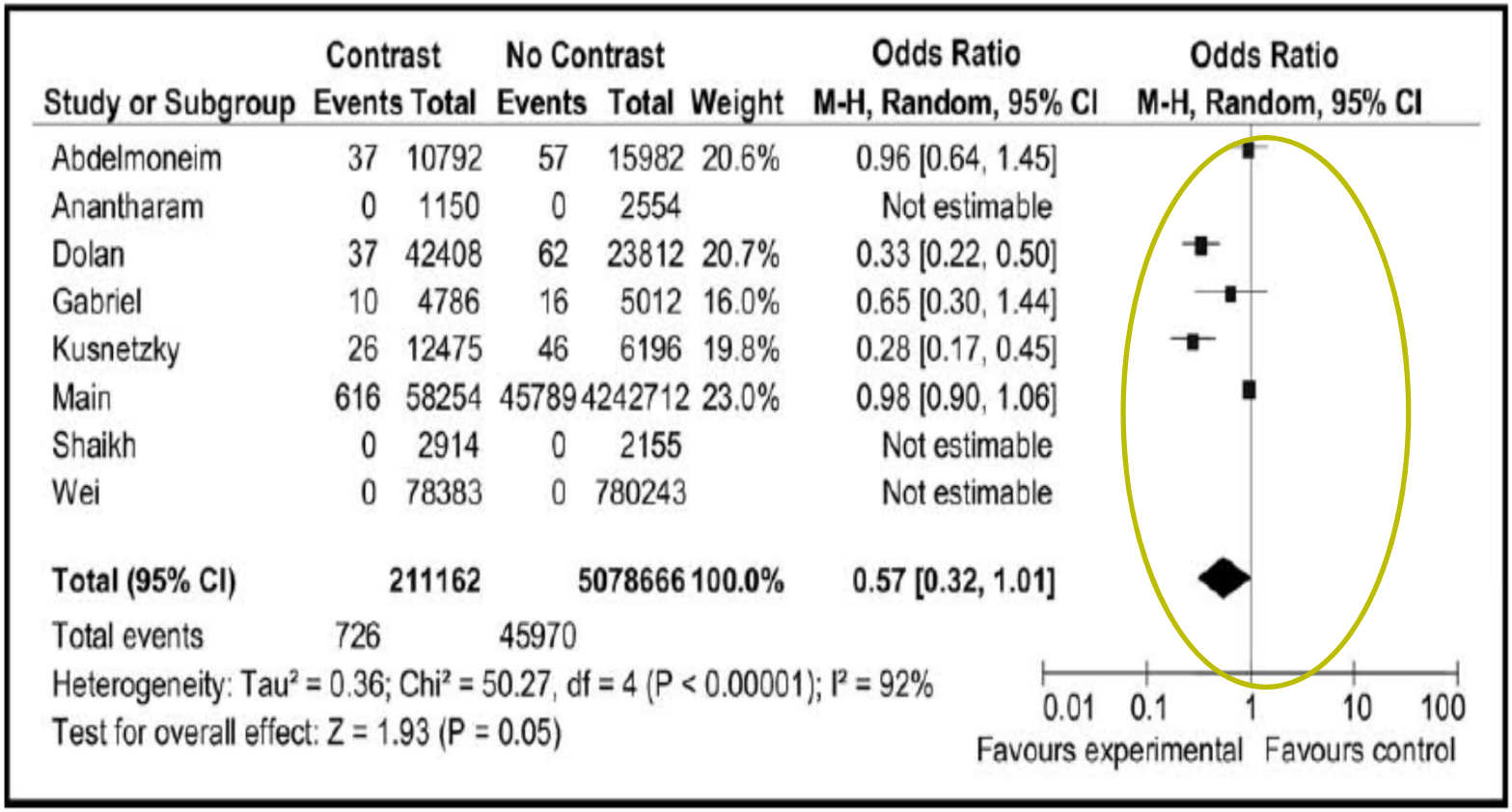
- **Khawaja et al. Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents. Am J Cardiol 2010;106:742-747.**
- **Wei K, et al. The safety of Definity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;11:1202-6.**
- **Herzog C.I et al. Incidence of Adverse Events Associated With Use of Perflutren Contrast Agents for Echocardiography. JAMA 2008; V299, No. 18:2023-5.**

Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents

- **211,162 patients selected from 8 studies (2008-10)**
- **Endpoints: MI and death**
- **Incidence of MI (4 studies) = 0.15% in CEUS vs. 0.2% non-CEUS**
- **Incidence of death (8 studies) = OR 0.57 (95% CI 0.32, 1.01)**
- **In all 8 studies: CEUS patients higher clinical acuity and co-morbidities (older, sicker, more CV risks)**
- **Conclusion: "No significant difference in the incidence of MI or death."**

Khawaja et al. Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents. Am J Cardiol 2010;106:742-747

Meta-analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents (pooled odds ratio for death)



Study or Subgroup	Contrast Events	Contrast Total	No Contrast Events	No Contrast Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelmoneim	37	10792	57	15982	20.6%	0.96 [0.64, 1.45]
Anantharam	0	1150	0	2554		Not estimable
Dolan	37	42408	62	23812	20.7%	0.33 [0.22, 0.50]
Gabriel	10	4786	16	5012	16.0%	0.65 [0.30, 1.44]
Kusnetzky	26	12475	46	6196	19.8%	0.28 [0.17, 0.45]
Main	616	58254	45789	4242712	23.0%	0.98 [0.90, 1.06]
Shaikh	0	2914	0	2155		Not estimable
Wei	0	78383	0	780243		Not estimable
Total (95% CI)		**211162**		**5078666**	**100.0%**	**0.57 [0.32, 1.01]**
Total events	726		45970			

Heterogeneity: Tau² = 0.36; Chi² = 50.27, df = 4 (P < 0.00001); I² = 92%

Test for overall effect: Z = 1.93 (P = 0.05)

Figure 2. Pooled OR for all-cause mortality across studies between patients undergoing and not undergoing contrast imaging.

Khawaja et al. Am J Cardiol 2010;106:742-747

Retrospective Safety Analysis of CEUS
Wei et al. American Society of Echocardiography

- **In 2008, the American Society of Echocardiography convened an expert panel**
- **Retrospective analysis of 78,383 doses of contrast ultrasound agents; Optison = 12,219**
- **0% deaths, 0% SAEs, and 0.0003% AEs (n = 4) reported for Optison**
- **5 centers recorded right ventricular systolic pressure measurements in >7,400 injections**
- **Serious allergic reactions: 0% rate for Optison**

Wei K, et al. The safety of Definity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;11:1202 -6.

Wei et al, 2008 Conclusion

- **The incidence of SARs to ultrasound contrast agents was lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests**

  "The Black Box warning effectively eliminated the use of ultrasound contrast agents in those whom these agents are of the greatest clinical benefit."

  "The results obtained in this study occurred without routine monitoring , and suggest… the [black box] recommendation for monitoring should be re-evaluated and potentially eliminated."

Wei K, et al. The safety of Definity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;11:1202 -6.

Retrospective Safety Analysis of CEUS Herzog et al.

- **Retrospective data review from over 112,776 echocardiograms; 16,025 received CEUS and observed for 30 minutes post infusion**
- **3,051 patients received Optison**
- **No deaths for Optison patients**
- **No AEs for Optison patients**
- **Conclusion: Incidence of serious, non-fatal reactions was similar to that of low-osmolar, iodinated contrast media**

Herzog C.I et al. Incidence of Adverse Events Associated With Use of Perflutren Contrast Agents for Echocardiography. JAMA 2008; V299, No, 18: 2023-5

Peer-reviewed Literature: Conclusions

- **There exists no safety signal based on peer-reviewed literature and new sponsor data**

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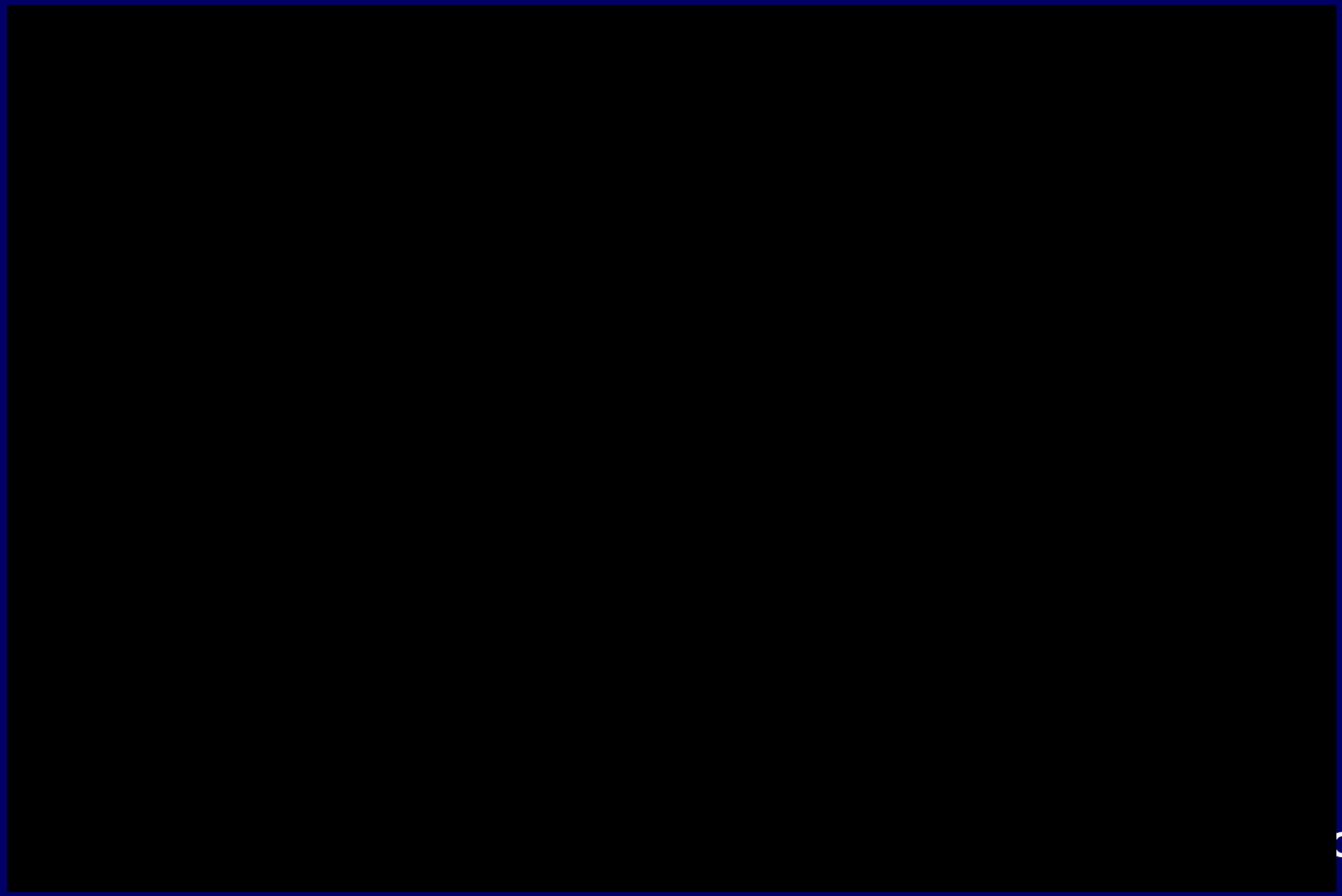
5.	Conclusions	Paul Sherwin, MD, PhD	GE Healthcare

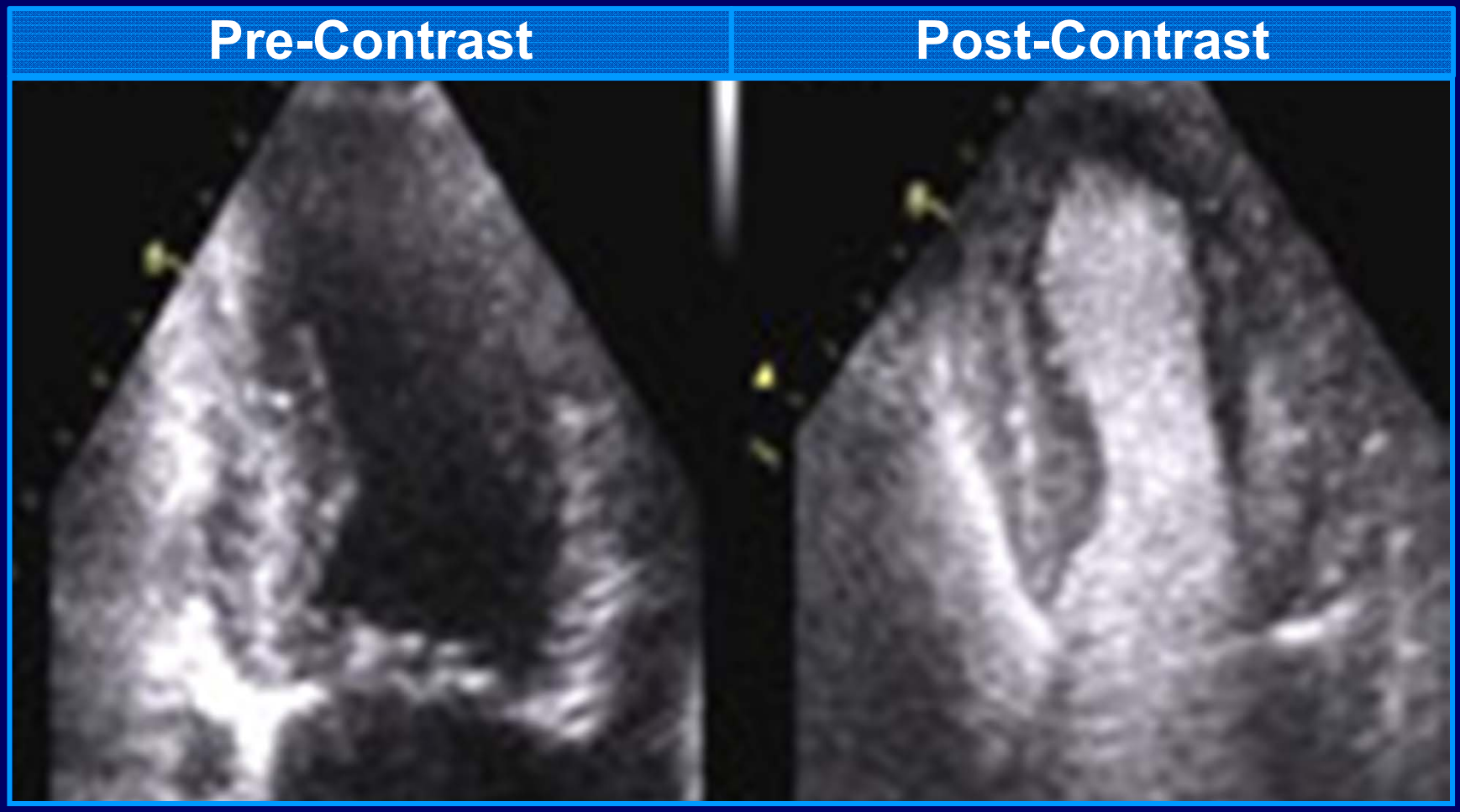
Why We Need Optison for Our Patients

- CEUS is critical for clinical decision-making
- Approximately 10-30% of echos are technically limited
- Accurate assessment of:
  - Left ventricular functional volumes
  - Ejection fraction
  - Intra-cavitary thrombus
  - Anatomic abnormalities (HCM, pseudo-aneurysm)
- Disease management: diagnosis, post-therapy monitoring of patients with:
  - Congestive heart failure
  - Coronary artery disease
  - Post-myocardial infarction

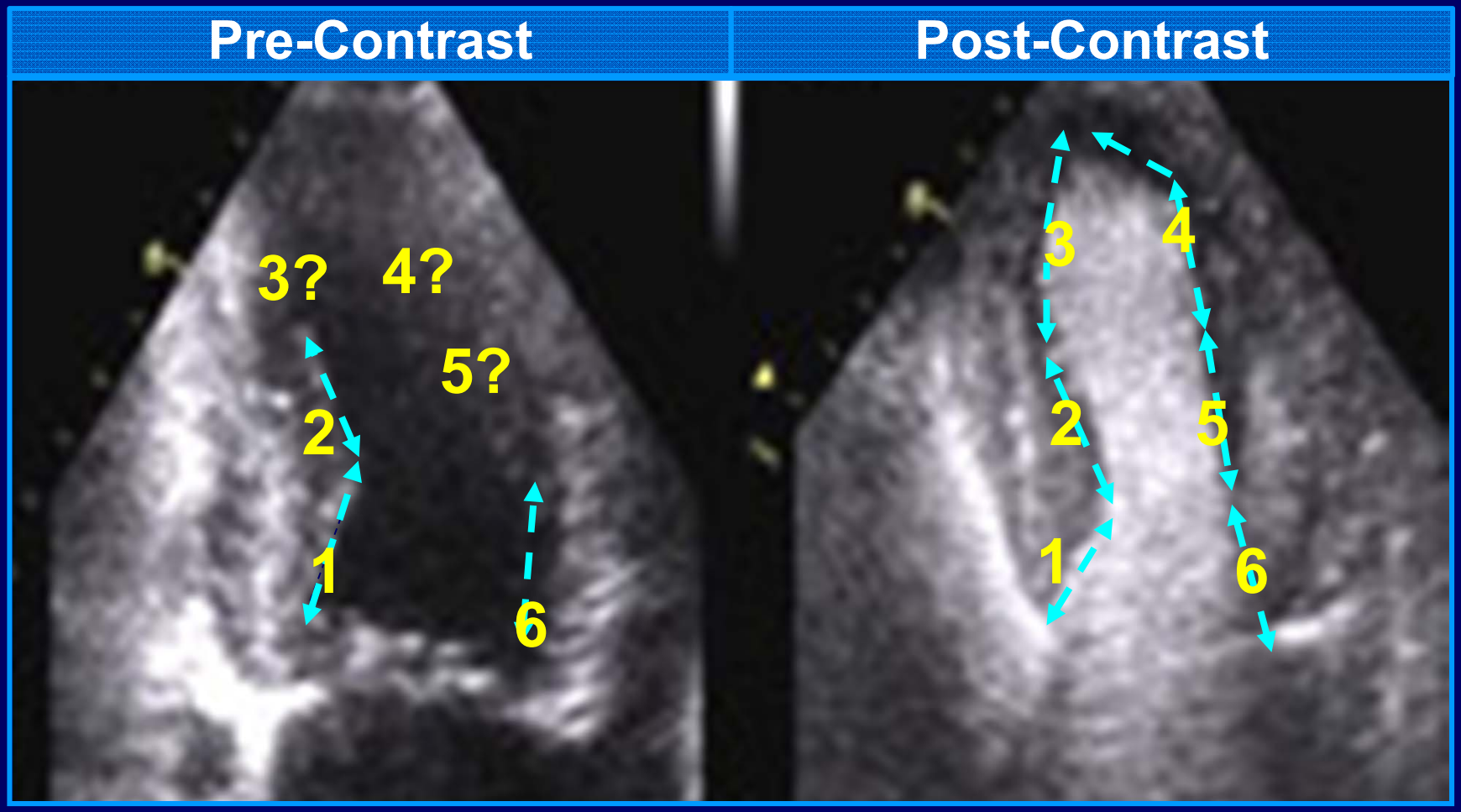
Value of CEUS in Practice: Enhanced Visualization Of The Cardiac Chambers



Endocardial Border Delineation Improved With Contrast Enhancement



Contiguous Segment Visualization Improved With Contrast Enhancement



Professional Practice Guidelines for CEUS Evidence-based Medicine

- American Society of Echocardiography Consensus 2000/2008
- American College of Cardiology/American Heart Association/American Society of Echocardiography 2003
- European Association of Echocardiography 2009
- Intersocietal Commission for Accreditation of Echocardiography Laboratories (ICAEL) 2010
- Ontario Health Technology Assessment Series 2010
- Appropriateness guidelines for use of CEUS: ACCF/ASE/AHA/ASNC/HRS/SCAI/SCCM/SCCT/SCMR/ ACCP 2011

ICAEL Accreditation Guidelines 2010
Stress Echo Testing Section 4.3.1 E

- **As Director of Echo Laboratory at Rush University: we perform ~15,000 echos/year and we are 1 of ~3,500 ICAEL accredited labs; therefore, we adhere to the guidelines:**

  "Contrast is indicated for use when two contiguous segments are not visualized as it provides greater accuracy in determining left ventricular function.

  Contrast must be used if this is not accomplished with harmonic imaging." **(specific reference to stress testing)**

ICAEL Standards www.icael.org/icael/main/icael_standards.htm

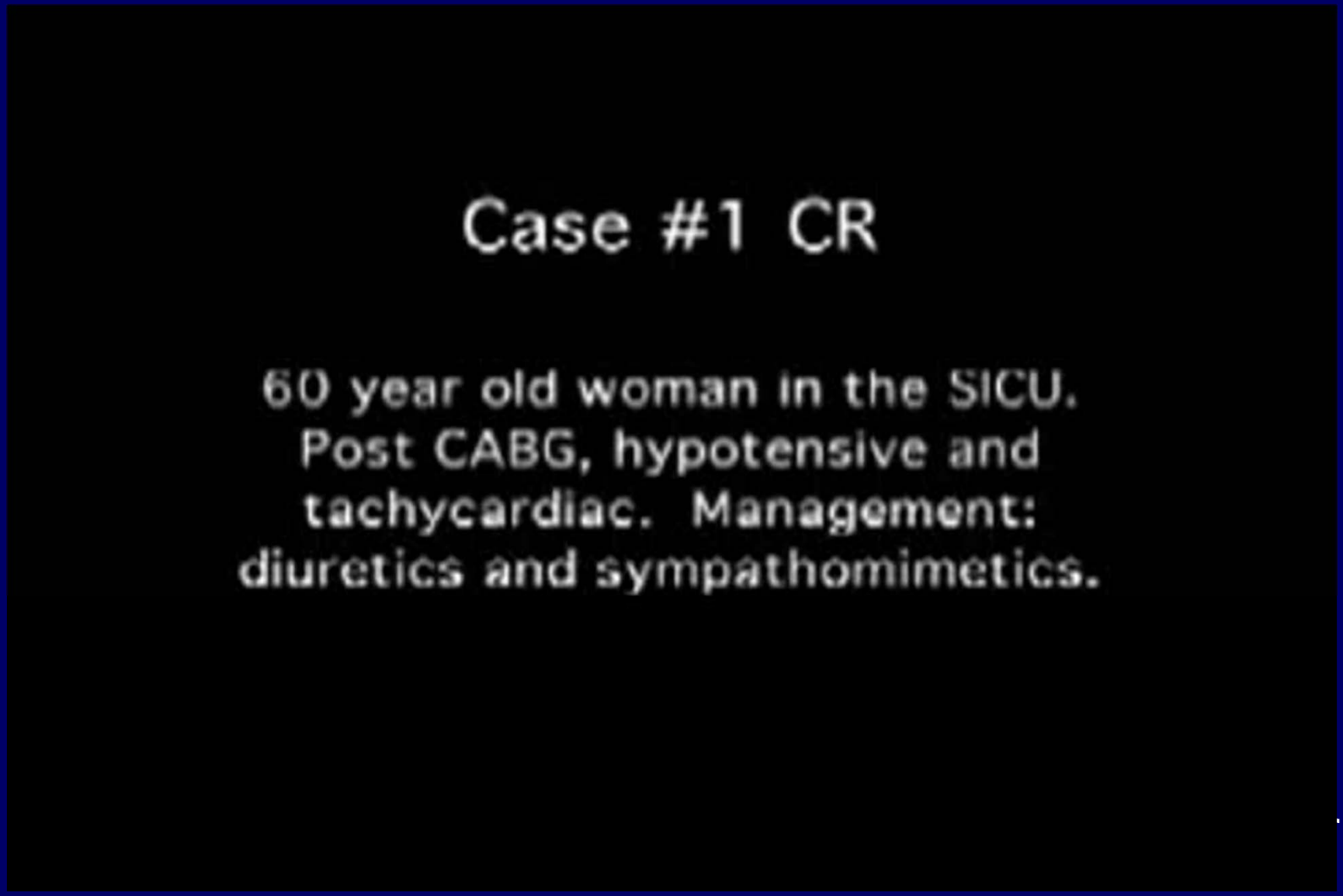
Medicine at the Bedside: CEUS Scenario

- **Suboptimal echocardiogram: UCA indicated**
- **Hospital personnel or family member asks:** ***"Did we inform the patient/family that we are using a Black Box drug?"***
- **As the echo lab director I discuss with patient/family**
  - **I cite evidence-based data showing that UCAs are safe, effective, reduce downstream testing, and avoid additional risks and ionizing radiation**
- **The patient/family decline the use of UCA based on Boxed Warning**
- **Patient goes to additional, higher-risk tests and ionizing radiation**

Optison Usage in the Critical Care Unit

- Pre-CEUS image led to wrong diagnosis/treatment
- CEUS led to correct diagnosis and changed therapy
- 60-yr-old woman in Surgical Intensive Care Unit
- Post-CABG, hypotensive, and tachycardic
- Technically difficult image
- Management: diuretics and sympathomimetics
- **Result:** Post-CEUS images changed the diagnosis and changed the therapy
- Typically observed on daily basis in every intensive care unit, clinic and outpatient setting

Optison Usage in the Surgical Intensive Care

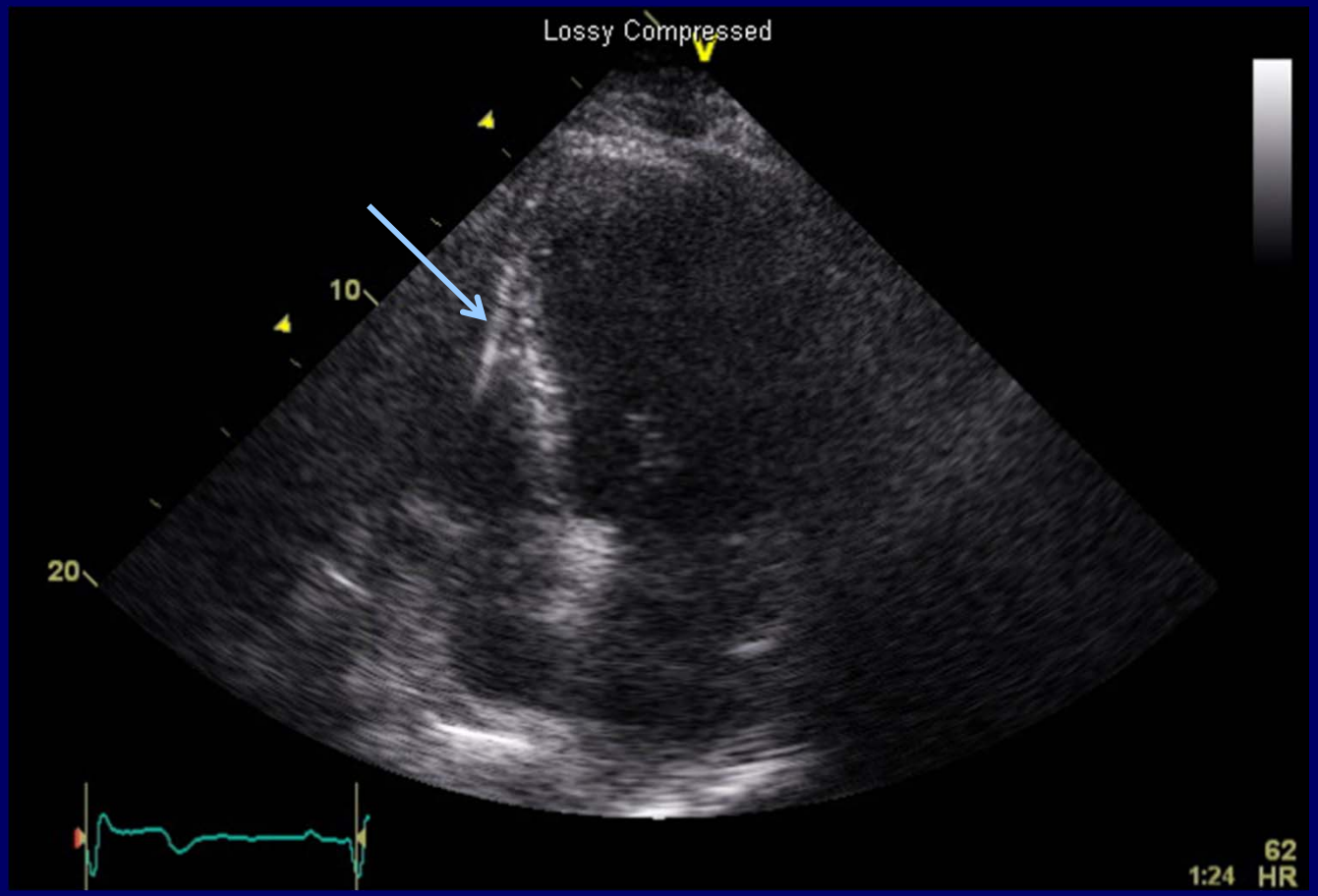


Optison Use in the Outpatient Clinic

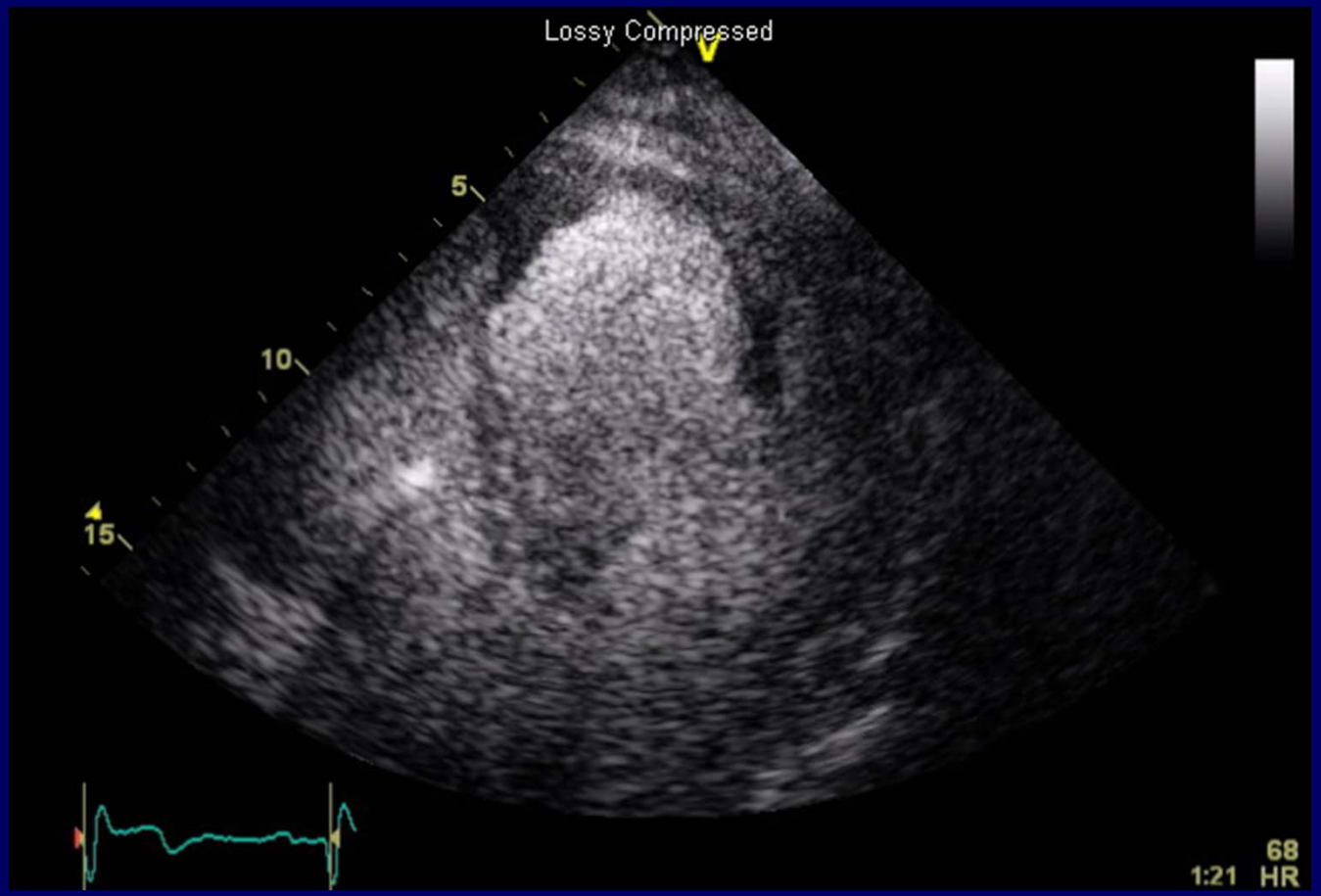
- 66-year-old man: routine defibrillator checkup
- Ejection fraction < 30%; high risk patient; defibrillator used to prevent sudden death
- Elevated pulmonary artery pressures >45 mmHg
- This patient presented with pulmonary hypertension and unstable cardiovascular conditions
- All clinical conditions that are listed in the Boxed Warning for use of Optison

Outpatient Use for CEUS

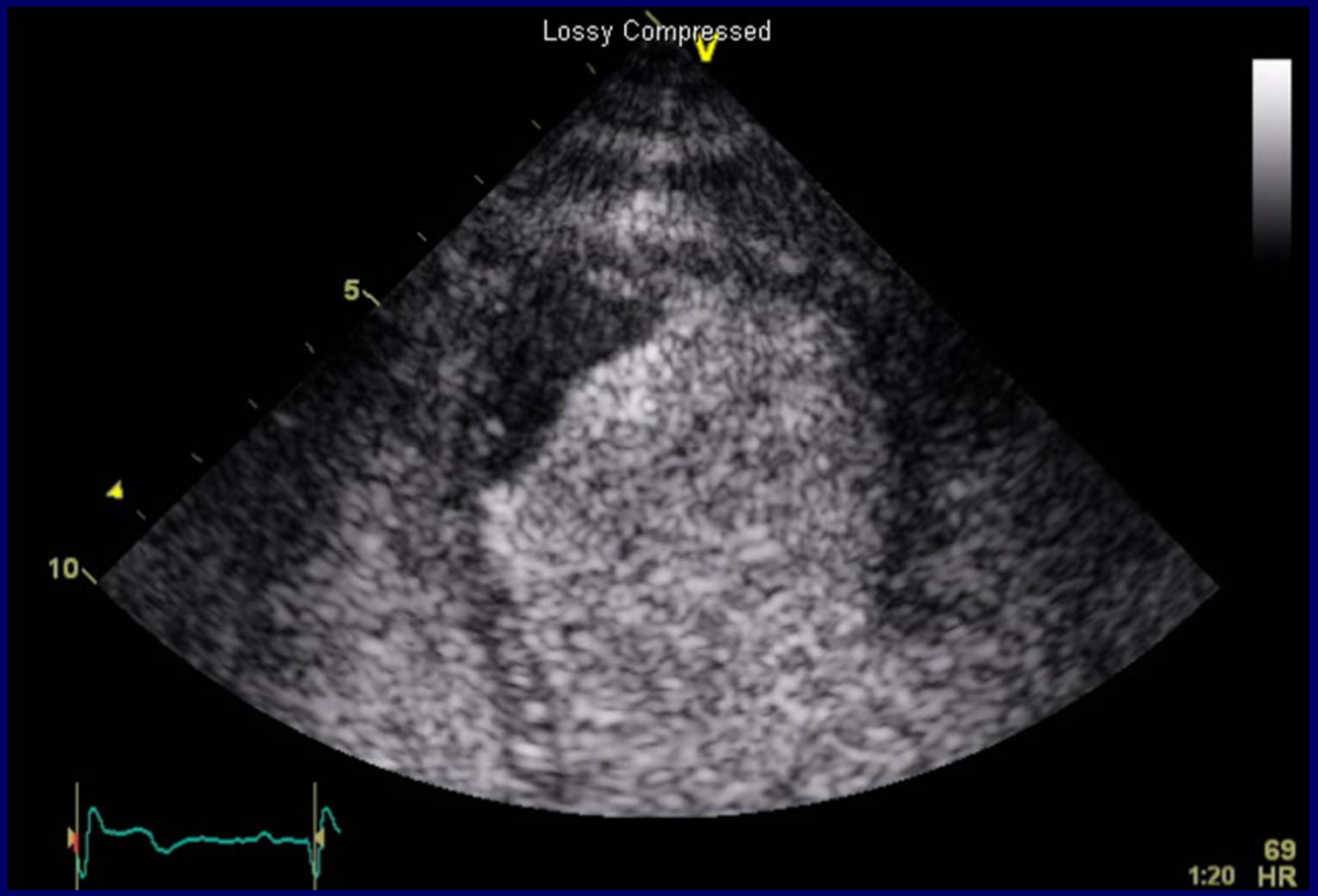
A technically limited baseline image led to a decision for the use of contrast...



With Contrast, a Large Defect in the Apex is Clearly Seen



With Contrast, a Large Defect in the Apex is Clearly Seen and Appeared Pedunculated



Conclusions

- Clear medical need for UCA and Optison
- Professional practice guidelines based on evidence-based medicine require CEUS
- There exists no safety signal based on peer-reviewed and evidence-based medicine
- 1.15 million Optison doses; no related deaths
- Boxed Warning limits use of CEUS resulting in negative impact on patient care
- Current Contraindications and Warnings sections suffice
- Removal of Boxed Warning is justified because the data demonstrate no evidence of a safety concern

Overview of Presentation

	Topic	Presenter	Affiliation
1.	Introduction and Optison Post-Marketing Safety Data	Paul Sherwin, MD, PhD	GE Healthcare
2.	Post-Marketing Clinical Studies of Optison Safety	Jonathan Goldman, MD, FACC, FASE	ICON, Clinical Research UCSF
3.	Peer-Reviewed Literature on Optison Human Safety	Steven Feinstein, MD, FACC, FESC	Rush University Medical Center
4.	Impact of Product Labeling on Patient Care	Steven Feinstein, MD, FACC, FESC	Rush University Medical Center
5.	Conclusions	Paul Sherwin, MD, PhD	GE Healthcare

Support for Removal of Boxed Warning

- **Post-marketing safety surveillance data**
  - **Very low event rate**
- **Clinical studies**
  - **No SARs or increase in mortality**
- **Literature**
  - **Use recommended in critical patients**
- **Clinical experience**
  - **Delays in diagnosis, higher-risk procedures**

Conclusions: Optison Label

- Boxed Warning based on data from 2007-2008
- Current data demonstrate safety of Optison
- Contraindications and Warnings sections of package insert sufficient
- Removal of Boxed Warning is justified because the data demonstrate no evidence of a safety concern
- Reformat Prescribing Information to better highlight Contraindications and Warnings

Optison™

(perflutren protein-type A microspheres injectable suspension)

GE Healthcare

Additional Q&A Material

Summary of Adverse Event Type by Optison Dose Stratification and Echocardiogram Type – Safety Pop

	Optison Dose (mL)					
	<5.0 mL		5.0-8.7 mL		>8.7 mL	
Adverse Event Type	Stress n/N (%)	Non-Stress n/N (%)	Stress n/N (%)	Non-Stress n/N (%)	Stress n/N (%)	Non-Stress n/N (%)
Cardiac	112/454 (25)	10/535 (2)	6/8 (75)	0/1 (0)	1/1 (100)	0/0
Pulmonary	68/454 (15)	0/535 (0)	0/8 (0)	0/1 (0)	0/1 (0)	0/0
ECG abnormalities[1]	76/454 (17)	5/535 (1)	5/8 (63)	0/1 (0)	1/1 (100)	0/0
Other	15/454 (3)	1/535 (<1)	3/8 (38)	0/1 (0)	0/1 (0)	0/0

N = number in dose group; n = number with AE type; % = 100*(n/N)
1 ECG abnormalities are s subset of Cardiac events

Summary of Adverse Event Type by Echocardiogram Type – Safety Population

Adverse Event Type	Stress Type [1]					
	Exercise n/N (%)	Dobutamine[2] n/N (%)	Adenosine n/N (%)	Total Stress n/N (%)	Non-Stress n/N (%)	Overall n/N (%)
Cardiac	50/250 (20)	70/216 (32)	0/2 (0)	120/466 (26)	10/536 (2)	130/1039 (13)
Pulmonary	54/250 (22)	14/216 (6)	0/2 (0)	68/466 (15)	0/536 (0)	68/1039 (7)
ECG abnormalitities[3]	33/250 (13)	49/216 (23)	0/2 (0)	82/466 (18)	5/536 (1)	87/1039 (8)
Other	7/250 (3)	11/216 (5)	0/2 (0)	18/466 (4)	1/536 (0)	20/1039 (2)

N = number with stress type; n = number with AE type; % = 100*(n/N)

1 Subjects many have more than one stress type

2 Some dobutamine subjects also received atropine

3 ECG abnormalities are a subset of Cardiac events

GE-191-004 Medical History

- **All 30 subjects had a medical history consistent with cardiac disease.**
- **Overall, 19 subjects had PA hypertension**
  - **12 had primary hypertension**
  - **7 had secondary hypertension due to Eisenmenger Syndrome (1), CAD (1), NICM (1), cardiomyopathy (1), CHF (1), s/p Phen-Fen use (1), and pulmonary vacuities (1)**

Statistical Analysis of PASP and PVR, Hemodynamic Population

Parameter	Time Point	Stratum	Least-Square Mean N	Optison	Least-Square Mean N	Control	Least-Square Mean Difference (Optison to Control) (95% Confidence Interval)
Change from baseline PASP (mm-Hg)	2 Min Post-Injection	Normal PASP	11	0.80	10	–0.09	0.89 (–3.26, 5.05)
		Elevated PASP	19	0.19	16	2.00	–1.81 (–5.02, 1.40)
		Combined	30	0.50	26	0.95	–0.46 (–3.08, 2.16)
	6 Min Post-Injection	Normal PASP	11	–0.02	11	0.26	–0.28 (–3.98, 3.42)
		Elevated PASP	18	–1.36	19	1.24	–2.60 (–5.42, 0.23)
		Combined	29	–0.69	30	0.75	–1.44 (–3.76, 0.89)
	10 Min Post-Injection	Normal PASP	10	–1.36	11	–0.60	–0.76 (–5.10, 3.58)
		Elevated PASP	19	–1.97	19	2.29	–4.26 (–7.55, –0.97)
		Combined	29	–1.66	30	0.84	–2.51 (–5.23, 0.22)
Change from baseline PVR (Wood units)	2 Min Post-Injection	Normal PASP	10	0.14	10	0.02	0.11 (–1.28, 1.51)
		Elevated PASP	15	0.03	13	0.17	–0.14 (–1.25, 0.97)
		Combined	25	0.08	23	0.10	–0.01 (–0.90, 0.88)
	6 Min Post-Injection	Normal PASP	10	–0.12	9	–0.18	0.05 (–1.34, 1.45)
		Elevated PASP	14	–0.31	17	–0.14	–0.18 (–1.25, 0.89)
		Combined	24	–0.22	26	–0.16	–0.06 (–0.94, 0.82)
	10 Min Post-Injection	Normal PASP	10	–0.10	9	–0.34	0.24 (–1.08, 1.55)
		Elevated PASP	15	–0.12	16	0.04	–0.16 (–1.17, 0.86)
		Combined	25	–0.11	25	–0.15	0.04 (–0.79, 0.87)

PASP = pulmonary artery systolic pressure; PVR = pulmonary vascular resistance